FGFR-selective tyrosine kinase inhibitors, such as infigratinib, show potency and selectivity for FGFR3 at pharmacologically relevant doses for the potential treatment of achondroplasia

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Purpose: Explore the publicly available literature to evaluate the dose dependency and toxicity profile of FGFR-selective TKIs in preclinical skeletal dysplasia models.

Methods:

- An in-vivo literature review was performed to identify any clinical data from studies of FGFR-selective TKIs in preclinical skeletal dysplasia models.
- Two major types of sources were searched on October 22, 2019:
  - Major databases (e.g., PubMed, Medline [NLM Catalog]) were searched for relevant articles from the past 10 years.
- Conference archives (e.g., ENDO, ESPE, ISDS, ASHG, ASBMR) were searched for relevant abstracts from the past 5 years.

Results:

- 14 publications were included in this review (Figure 1).
- 85% of the publications were identified through the initial search, with 32% remaining after screening for date and duplicates.
- 310 publications were excluded based on the abstract and standard, leaving 16 remaining to assess full text.
- Of the 16 publications reviewed for full texts, four were excluded; 96% of the full-text publications included one of the major FGFR-selective TKIs.
- Two additional publications found through review of identified publications were included due to direct relevance.

Conclusions:

- While both studies suggest toxicity with FGFR-selective TKIs, this was produced at doses significantly higher than pharmacologically relevant doses for the treatment of achondroplasia or other skeletal dysplasias.
- In addition, the skeletal dysplasia mouse model treated with doses of infigratinib showed increased growth in long bones and femoral length with a good dose-response relationship. No toxic effects were observed at these low but efficacious doses.

Clinical relevance:

- Given the totality of evidence, low-dose infigratinib appears to be a potentially safe option for further development in children with achondroplasia.

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References: